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Critical Health Issues Associated with Review of the Scientific Criteria for Carbon Monoxide

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16. ABSTRACT

The Clean Air Act (CAA) requires periodic review of existing criteria that form the basis for carbon monoxide (CO) air quality standards. These air quality criteria are to reflect the latest scientific information useful in indicating the kind and extent of all identifiable effects on pubic health that may be expected from the presence of CO in ambient air. In keeping with the requirements of the CAA, the U.S. Environmental Protection Agency has stated to review the criteria for CO. A number of critical issues germane to this review are presented. Additional session papers provide more detailed discussion of these issues. This paper discusses specific health issues pertaining to: (1) mechanisms of action of CO, particularly an evaluation of intracellular mechanisms secondary to impaired oxygen delivery caused by the formation of carboxyhemoglobin (COHb); (2) exposure assessment, including an evaluation of the accuracy and reliability of different methods for determining COHb; and (3) specific health effects occurring in groups of individuals considered to ba at greatest risk to CO at ambient or near-ambient exposure levels including a reevaluation of previous dose-response functions for CO utilizing the information gained from recently completed studies. These critical issues will need to be resolved in order to determine the extent to which adverse effects are occurring in the population, particularly at the lower COHb levels of greatest interest to standard setting.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

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CRITICAL HEALTH ISSUES ASSOCIATED WITH REVIEW OF THE SCIENTIFIC CRITERIA FOR CARBON MONOXIDE

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INTRODUCTION*

Two sections of the Clean Air Act (CAA) govern the establishment, review, and revision of national ambient air quality standards (NAAQS). Section 108 (42 U.S.C. 7408) directs the Administrator of the Environmental Protection Agency (EPA) to identify pollutants that may reasonably be anticipated to endanger public health or welfare and to issue air quality criteria for them. These air quality criteria are to reflect the latest scientific information useful in indicating the kind and extent of all identifiable effects on public health or welfare that may be expected from the presence of the pollutant in ambient air.

Section 109(a) of the CAA (42 U.S.C. 7409) directs the Administrator of EPA to propose and promulgate primary and secondary NAAQS for pollutants identified under section 108. Section 109(b)(1) defines a primary standard as one the attainment and maintenance of which in the judgment of the Administrator, based on the criteria and allowing for an adequate margin of safety, is requisite to protect the public health. The secondary standard, as defined in section 109(b)(2), must specify a level of air quality the attainment and maintenance of which in the judgment of the Administrator, based on the criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of the pollutant in ambient air. Section 109(d) of the CAA (42 U.S.C. 7409) requires periodic review and, if appropriate, revision of existing criteria and standards. If, in the Administrator's judgment, the Agency's review and revision of criteria make appropriate the proposal of new or revised standards, such standards are to be revised and promulgated in accordance with section 109(b). Alternately, the Administrator may find that revision of the standards is inappropriate and conclude the review by leaving the existing standards unchanged.

In keeping with the requirements of the CAA, the Environmental Criteria and Assessment Office of EPA has started to review and revise once again the criteria for carbon monoxide (CO). New data on the health and air quality aspects of CO exposure have become available since completion of the previous Air Quality Criteria Document (U.S. Environmental Protection Agency, 1979) and an addendum to that Document (U.S. Environmental Protection Agency, 1984a). The information presented in this paper will review the regulatory and scientific background for the current CO NAAQS and discuss some of the critical health issues germane to review of the scientific basis for those standards.

REGULATORY BACKGROUND*

On April 30, 1971 EPA promulgated identical primary and secondary NAAQS for CO at levels of 9 ppm for an 8-hr average and 35 ppm for a 1-hr average, not to be exceeded more than once per year. The scientific basis for the primary standard, as described in the first criteria document (National Air Pollution Control Administration, 1970), was a study suggesting that low levels of CO exposure resulting in carboxyhemoglobin (COHb) concentrations of 2 to 3% were associated with neurobehavioral effects in exposed subjects (Beard and Wertheim, 1967).

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* This text is excerpted and adapted from "Review of the National Ambient Air Quality Standards for Carbon Monoxide; Final Rule" (50 FR 37484, September 13, 1985)

In accordance w
revised the criteria
On August 18, 1980 EP

TABLE 1. NATION

Date of Promulgation
September 13, 1985

[a]1 ppm = 1.145 mg/m[3],
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In accordance with sections 108 and 109 of the CAA, EPA has reviewed and revised the criteria upon which the existing NAAQS for CO (Table 1) are based. On August 18, 1980 EPA proposed certain changes in the standards (45 FR 55066)

TABLE 1. NATIONAL AMBIENT AIR QUALITY STANDARDS FOR CARBON MONOXIDE

Date of Promulgation	Primary NAAQS	Averaging Time
September 13, 1985	9 ppm[a] (10 mg/m^3) 35 ppm[a] (40 mg/m^3)	8-hr[b] 1-hr[b]

[a] 1 ppm = 1.145 mg/m^3, 1 mg/m^3 = 0.873 ppm @ 25°C, 760 mm Hg.

[b] Not to be exceeded more than once per year.

based on scientific evidence reported in the revised criteria document for CO (U.S. Environmental Protection Agency, 1979). Such evidence indicated that the Beard and Wertheim (1967) study was no longer considered to be a sound scientific basis for the standard. Additional medical evidence accumulated since 1970, however, indicated that aggravation of angina pectoris and other cardiovascular diseases would occur at COHb levels as low as 2.7 to 2.9%. The proposed changes included (1) retaining the 8-hr primary standard level of 9 ppm, (2) revising the 1-hr primary standard level from 35 ppm to 25 ppm, (3) revoking the existing secondary CO standards (since no adverse welfare effects have been reported at or near ambient CO levels), (4) changing the form of the primary standards from deterministic to statistical, and (5) adopting a daily interpretation for exceedances of the primary standards, so that exceedances would be determined on the basis of the number of days on which the 8- or 1-hr average concentrations are above the standard levels.

The 1980 proposal was based in part on health studies conducted by Dr. Wilbert Aronow. In March of 1983 EPA learned that the Food and Drug Administration (FDA) had raised serious questions regarding the technical adequacy of several studies conducted by Dr. Aronow on experimental drugs, leading FDA to reject use of the Aronow drug study data. Therefore, EPA convened an expert committee to examine the Aronow CO studies before any final decisions were made on the NAAQS for CO. The committee concluded that EPA should not rely on Dr. Aronow's data due to concerns regarding the research which substantially limited the validity and usefulness of the results.

An addendum to the 1979 criteria document for CO (U.S. Environmental Protection Agency, 1984a) reevaluated the scientific data concerning health effects associated with exposure to CO at or near ambient exposure levels in light of the committee recommendations and taking into account new findings reported beyond those previously reviewed. (These data are summarized in the following section.) On September 13, 1985 EPA issued a final notice (50 FR 37484) announcing retention of the existing primary NAAQS for CO and rescinding the secondary NAAQS for CO.

SCIENTIFIC BACKGROUND

The following is a summary of the scientific basis for the current CO NAAQS. These key points were derived from a revised evaluation of the health effects of carbon monoxide that was released as an addendum (U.S. Environmental Protection Agency, 1984a) to the previous air quality criteria document for CO (U.S. Environmental Protection Agency, 1979).

Mechanisms of Action

The binding of carbon monoxide to hemoglobin, producing carboxyhemoglobin (COHb) and decreasing the oxygen-carrying capacity of blood, appears to be the principle mechanism of action underlying the induction of toxic effects of low-level CO exposures. The precise mechanisms by which toxic effects are induced via COHb formation are not yet fully understood, but likely include the induction of a hypoxic state in many tissues of diverse organ systems. Alternative or secondary mechanisms of CO-induced toxicity (besides COHb) have been hypothesized, but none have yet been demonstrated to operate at relatively low (near-ambient) CO exposure levels. Blood COHb levels, then, are currently accepted as representing a useful physiological marker by which to estimate internal CO burdens due to the combined contribution of (1) endogenously derived CO and (2) exogenously derived CO resulting from exposure to external sources of CO. COHb levels likely to result from particular patterns (concentrations, durations, etc.) of external CO exposure can be reasonably well estimated from equations developed by Coburn et al. (1965) as demonstrated in Figure 1.

CO Exposure Levels

Evaluation of human CO exposure situations indicates that occupational exposures in some workplaces or exposures in homes with faulty combustion appliances can exceed 100 ppm CO, often leading to COHb levels of 10% or more with continued exposure. In contrast, such high exposure levels are much less commonly encountered by the general public exposed under ambient conditions. More frequently, exposures to less than 25 to 50 ppm CO for any extended period of time occur among the general population and, at the low exercise levels usually engaged in under such circumstances, resulting COHb levels most typically remain 2 to 3% among nonsmokers. Those levels can be compared to the physiologic norm for nonsmokers, which is estimated to be in the range of 0.3 to 0.7% COHb. Baseline COHb concentrations in smokers, however, average 4 percent with a usual range of 3 to 8 percent, reflecting absorption of CO from inhaled smoke.

Health Effects of Low Level CO Exposures

Four types of health effects reported or hypothesized to be associated with CO exposures (especially those producing COHb levels below 10%) were evaluated in the last review of the CO NAAQS (U.S. Environmental Protection Agency, 1984a): (1) cardiovascular effects; (2) neurobehavioral effects; (3) fibrinolysis effects; and (4) perinatal effects. Data available at that time (Table 2) demonstrated an association between cardiovascular and neurobehavioral effects at relatively low-level CO exposures. Much less clear evidence existed to indicate that other types of health effects were associated with low-level CO exposures.

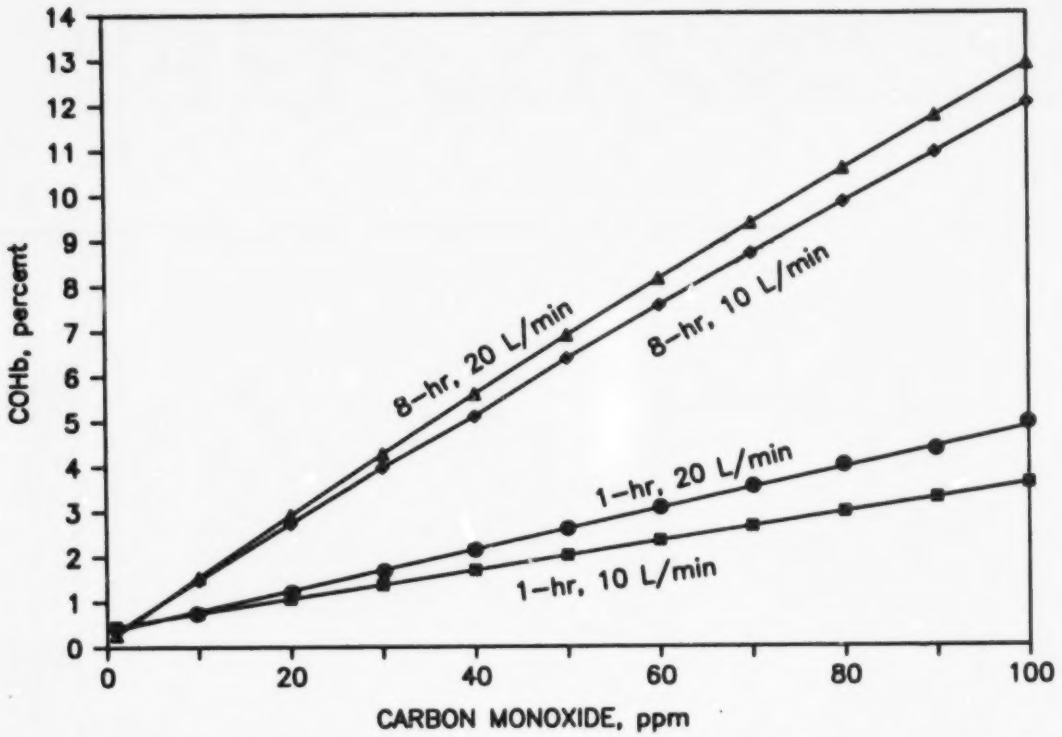

Figure 1. Predicted %COHb levels resulting from 1- and 8-hr exposures to carbon monoxide at rest (10 L/min) and with light exercise (20 L/min); based on the Coburn-Forster-Kane equation (Coburn et al., 1965) using the following assumed parameters for nonsmoking adults: altitude = 0 ft; initial COHb level = 0.5 %; Haldane constant = 218; blood volume = 5.5 L; hemoglobin level = 15 g/100 ml; lung diffusivity = 30 ml/torr/min; endogenous rate = 0.007 ml/min.

TABLE 2. LOWEST OBSERVED EFFECT LEVELS FOR HUMAN HEALTH EFFECTS ASSOCIATED WITH LOW LEVEL CARBON MONOXIDE EXPOSURE

Effects	COHb Concentration, percent[a]	References
Statistically significant decreased (~3-7%) work time to exhaustion in exercising young healthy men	2.3-4.3	Horvath et al. (1975) Drinkwater et al. (1974)
Statistically significant decreased exercise capacity (i.e., shortened duration of exercise before onset of pain) in patients with angina pectoris and increased duration of angina attacks	2.9-4.5	Anderson et al. (1973)
Statistically significant decreased maximal oxygen consumption and exercise time during strenuous exercise in young healthy men	5-5.5	Klein et al. (1980) Stewart et al. (1978) Weiser et al. (1978)
No statistically significant vigilance decrements after exposure to CO	Below 5	Haider et al. (1976) Winneke (1974) Christensen et al. (1977) Benignus et al. (1977) Putz et al. (1976)
Statistically significant diminution of visual perception, manual dexterity, ability to learn, or performance in complex sensorimotor tasks (such as driving)	5-17	Bender, et al. (1971) Schulte (1973) O'Donnell et al. (1971) McFarland et al. (1944) McFarland (1973) Putz et al. (1976) Salvatore (1974) Wright et al. (1973) Rockwell and Weir (1975) Rummo and Sarlanis (1974) Putz et al. (1979) Putz (1979)
Statistically significant decreased maximal oxygen consumption during strenuous exercise in young healthy men	7-20	Ekblom and Huot (1972) Pirnay et al. (1971) Vogel and Gleser (1972)

[a]The physiologic norm (i.e., COHb levels resulting from the normal catabolism of hemoglobin and other heme-containing materials) has been estimated to be in the range of 0.3 to 0.7% (Coburn et al., 1963).

Source: U.S. Environmental Protection Agency (1984b)

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Cardiovascular Effects In regard to cardiovascular effects, decreased oxygen uptake and resultant decreased work capacity under maximal exercise conditions have been clearly shown to occur in healthy young adults starting at 5.0% COHb; and several studies observed small decreases in work capacity at COHb levels as low as 2.3 to 4.3%. These cardiovascular effects may have health implications for the general population in terms of potential curtailment of certain physically demanding occupational or recreational activities under circumstances of sufficiently high CO exposure. However, of greater concern at more typical ambient CO exposure levels were certain cardiovascular effects (i.e., aggravation of angina symptoms during exercise) likely to occur in a smaller, but sizeable, segment of the general population. This group, chronic angina patients, is presently viewed as the most sensitive risk group for CO exposure effects, based on evidence for aggravation of angina occurring in patients at COHb levels of 2.9 to 4.5% COHb. Such aggravation of angina is thought to represent an adverse health effect for several reasons articulated in the 1980 proposal preamble (45 FR 55066), and the Clean Air Scientific Advisory Committee (CASAC) concurred with EPA's judgment on this matter. Dose-response relationships for cardiovascular effects in coronary artery disease patients remain to be more conclusively defined, and the possibility cannot be ruled out at this time that such effects may occur at levels below 2.9% COHb (as hinted at by the results of the now-questioned Aronow studies). New studies are, therefore, currently being evaluated to determine the effects of CO on aggravation of angina at levels in the range of 2 to 6% COHb.

Neurobehavioral Effects No reliable evidence demonstrating decrements in neurobehavioral function in healthy young adults has been reported at COHb levels below 5%. Much of the research at 5% COHb did not show any effect even when behaviors similar to those affected in other studies were involved. However, investigators failing to find CO decrements at 5% or higher COHb levels may have utilized tests not sufficiently sensitive to reliably detect small effects of CO. From the empirical evidence, then, it can be said that the COHb levels in the 5% range do produce decrements in neurobehavioral function. It cannot be said confidently, however, that COHb levels lower than 5% would be without effect. One important point made in the 1979 criteria document should be reiterated here. Only young, healthy adults have been studied using demonstrably sensitive tests and COHb levels at 5% or greater. The question of groups at special risk for neurobehavioral effects of CO, therefore, has not been explored. Of special note are those individuals who are taking drugs which have primary or secondary depressant effects which would be expected to exacerbate CO-related neurobehavioral decrements. Other groups at possibly increased risk for CO-induced neurobehavioral effects are the aged and ill but these groups, also, have not been evaluated for such risk.

Other Health Effects Only relatively weak evidence points towards possible CO effects on fibrinolytic activity and, then, generally only at rather high CO exposure levels. Similarly, whereas certain data also suggest that perinatal effects (e.g. reduced birth weight, slowed postnatal development, Sudden Infant Death Syndrome) are associated with CO exposure, insufficient evidence presently exists by which to either qualitatively confirm such an association in humans or to establish any pertinent exposure-effect relationships.

CRITICAL HEALTH ISSUES

Based on the scientific evidence currently evaluated in air quality criteria documents (U.S. Environmental Protection Agency, 1979, 1984a), potentially adverse health effects of CO have been demonstrated to occur at COHb levels in the range of 2.3 to 20 percent (see Table 2). Several critical health issues, however, have developed during the current review of the scientific criteria for carbon monoxide air quality standards that will need to be resolved in order to determine the extent to which adverse effects are occurring in the population, particularly at the lower COHb levels of greatest interest to standard setting (≤5 percent). The following section will focus on specific health issues pertaining to (1) mechanisms of action of CO, (2) exposure assessment, including the measurement of CO in blood, and (3) specific health effects occurring in groups of individuals considered to be at greatest risk to CO at ambient or near-ambient exposure levels. Other issues pertaining to the monitoring of CO concentrations found in ambient air and their relationship to exposure of the general population are also important but they will not be addressed in this paper.

Mechanisms of Action of Carbon Monoxide

The accepted mechanisms of action underlying the potentially toxic effects of low-level CO exposure continue to be the decreased oxygen-carrying capacity of blood and subsequent interference of oxygen release at the tissue level that is caused by the binding of CO with hemoglobin, producing COHb. The resulting impaired delivery of oxygen can interfere with cellular respiration and cause tissue hypoxia.

Review of the newer information on mechanisms of action of CO has focused on the possibility that secondary mechanisms that can also impair cellular respiration may be occurring at relatively low (near-ambient) CO exposure levels. Approximately 10 to 50 percent of the total body burden of CO can be distributed to extravascular sites, suggesting that intracellular uptake of CO may contribute to CO-induced toxicity. It is uncertain, however, if intracellular uptake of CO occurs at low levels of COHb or if it would be likely to contribute to the physiological effects of CO.

Carbon monoxide will bind to intracellular hemoproteins such as myoglobin, metalloenzymes (e.g., cytochrome oxidase), mixed function oxidases (e.g., cytochrome P-450), tryptophan oxygenase, and dopamine hydroxylase. Binding to CO would be favorable under conditions of low intracellular PO_2, particularly in brain and myocardial tissue where intracellular PO_2 decreases with increasing COHb levels. The most likely hemoproteins to be partially inhibited at relevant levels of COHb are myoglobin (Mb), found predominantly in heart and skeletal muscle, and cytochrome oxidase. The physiological significance of CO uptake by myoglobin is uncertain at this time but sufficient concentrations of COMb could potentially limit maximal oxygen uptake of exercising muscle. Although there is suggestive evidence for significant binding of CO to cytochrome oxidase in heart and brain tissue, it is unlikely that any significant CO binding would occur at low COHb levels. Therefore, further research is still needed to determine if secondary, intracellular mechanisms will occur at exposure concentrations found in ambient air.

Exposure Assessment

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Exposure Assessment

The best indicator of exposure to CO continues to be the direct measurement of COHb in blood. There are, however, a number of issues regarding measurement techniques for COHb that have been raised during the review of the CO air quality criteria document now in progress. For many years, routine clinical laboratory measurements of COHb were commonly made using the IL 182 and it successor, the IL 282 CO-Oximeter (Instrumentation Laboratory, Inc., Lexington, MA,) which is a spectrophotometric instrument. Another instrument for COHb measurement that has become more widely used in laboratory settings is the gas chromatograph. Recent efforts to compare these two methods of COHb measurement have indicated that the high correlation seen over a wide range of concentrations (0 to >20 percent) becomes much worse at COHb levels <5 percent because of an apparent instrument offset or potential error. Thus, there has been concern about the relative accuracy and precision of the COHb measurements at levels that are of particular concern to the CO NAAQS review. Further, ongoing work is needed in order to determine (1) which method should be used to accurately quantify low levels of COHb, (2) if there is a scientifically acceptable way to compare COHb measurements made by different instruments across different laboratories, and (3) the relationship of measured COHb values and those derived from modeling efforts based on actual CO exposures in the general population.

Most "real-life" exposures to CO are to concentrations that vary with time and are experienced by people with differing physiological attributes and at varying exercise levels. Direct measurements of COHb are not readily available in the general population exposed to CO under these conditions. Mathematical models, therefore, have been developed to predict COHb levels from known CO exposures under a variety of circumstances. The most used model for COHb formations is still the Coburn-Forster-Kane equation (CFKE) developed by Coburn et al. (1965). The COHb levels predicted by this equation have been generally accepted as the best available estimates of COHb levels likely to result from varying CO concentrations, exposure durations, and exercise levels. Further research, however, is needed to evaluate the predictive capabilities of the CFKE in individuals exposed to low concentrations of CO leading to COHb levels of less than 10 percent. Of particular interest is the variation of predicted COHb in a population with a given pattern of CO exposure involving frequent concentration variations. In addition, the CFKE needs to be evaluated for applications to CO-susceptible subjects, such as patients with cardiovascular or pulmonary disease. Clinical evaluation of CO uptake by these individuals should be considered.

Epidemiology studies have suggested the possibility that increased mortality from heart attacks and increased cardiovascular complaints may be associated with ambient concentrations of CO. Unfortunately, due to inadequate characterization of exposure as well as other limitations, inconclusive results have been obtained from existing studies. The availability of both personal exposure monitors for CO and ambulatory EKG monitoring techniques have made it possible to design epidemiology studies to determine whether ambient CO exposures are related to serious or irreversible cardiovascular effects. It would be desirable, therefore, to obtain CO exposure data on CO-susceptible individuals in order to characterize their risk from elevated levels of COHb. Potentially susceptible individuals include infants, the elderly, and patients with known cardiovascular diseases.

Effects on the Cardiovascular System

Scientific support for the current NAAQS for carbon monoxide (CO) is based primarily on studies of patients with stable angina pectoris (chest pain) from coronary artery disease. Although it is assumed that the development of angina reflects adverse effects of myocardial metabolism, specific research supporting the validity of this assumption is lacking. For example, little is known about the reproducibility or reoccurrence of this disease. Nevertheless, time to onset of angina and the duration of angina is a measurable outcome which needs to be defined precisely as well as more objective methods, such as continuous EKG tracing for ST depression and arrhythmias and measurement of ventricular function using a gamma camera or thallium scan. In view of questions concerning the validity of angina studies by Aronow et al., additional data are clearly needed in order to (1) provide more reliable dose-response information in individuals with stable angina, (2) allow a better determination of the level of COHb necessary to cause adverse effects in the sensitive population, and (3) ultimately set an appropriate level for the CO NAAQS.

In response to this need, additional studies have recently been completed by a number of independent laboratories to identify the relationship between COHb and aggravation of preexisting chronic heart disease. Three of these studies have now been published (Sheps et al., 1987; Adams et al., 1988; Kleinman et al., 1989) and a forth major study has been submitted for publication (CO Multicenter Study, conducted by the Health Effects Institute). Results from these studies are being presented in separate papers at this session. Collectively, all four studies will provide new information on the likelihood that patients exposed to CO will experience angina earlier during exercise. Levels of COHb across the studies range from 2.7 to 5.9 percent, as measured by the spectrophotometric method (CO-Oximeter). An evaluation of these data is ongoing as part of the overall review of the scientific basis for the CO NAAQS. Any potential differences in the results between these studies will be primarily due to either the patient population studied or to the experimental design of the study itself.

Heart attack is the leading cause of death in the United States. In 1985 alone, over 540,000 deaths were attributed to coronary artery disease and over 4.8 million people alive at that time were estimated to have a history of heart attack, angina, or both (American Heart Association, 1988). Today that estimate may be as high as 6 to 7 million individuals inflicted with coronary artery disease. A major question that will become important in the evaluation of all the clinical studies involving subjects with coronary heart disease is whether the study population is representative of this broad group of patients with angina and, therefore, is applicable to the subpopulation of potentially susceptible individuals that are routinely exposed to ambient levels of CO. The possibility of studying the effects of CO in a more representative group of patients with coronary heart disease should be investigated. Recent changes in the treatment of coronary artery disease indicates that the sensitive subpopulation of angina patients may be changing from one of untreated patients to one of angina patients who have had coronary artery bypass or balloon angioplasty. The susceptibility of this new population to CO may not be the same. In addition, there is a greater likelihood of increased risk to CO exposure in a virtually unknown group of individuals who have silent ischemia (no symptomatic episodes of chest pain).

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Additional research is needed to determine dose-response relationships for the acute effects of CO in other potentially susceptible groups. Patients with arteriosclerosis of the arteries of the lower limbs who develop intermittent claudication are analogous to patients with angina and could be studied in a similar manner. Research is needed to determine dose-response relationships for cardiovascular effects in individuals with ventricular arrhythmias. Patients with anemia may be susceptible to increased levels of COHb, since CO would further reduce the already compromised arterial oxygen content of the blood. Patients with chronic obstructive pulmonary disease and those with congestive heart failure should also be studied to determine if they are at increased risk to low levels of CO exposure.

Other cardiovascular effects of low-level CO exposure, particularly with prolonged or chronic exposure, have not been demonstrated. Previous studies on laboratory animals that were reviewed in the last criteria document failed to clearly link CO exposure with atherogenesis and the development of arteriosclerosis. Newer data published since then still fail to conclusively prove an atherogenic effect of exposue to low concentrations of CO despite strong evidence from epidemiology studies showing an association between cigarette smoke and increased risk for arteriosclerosis. Other components of cigarette smoke (e.g., nicotine) as well as other risk factors (e.g., diet) may also promote atherogenesis, making it difficult to attribute the atherogenic effects of cigarette smoke to CO alone.

Neurobehavioral Effects

Neurobehavioral effects of CO exposure, such as (1) hand-eye coordination (compensatory tracking), (2) detection of infrequent events (vigilance), and visual system sensitivity have been reported in healthy young adults at COHb levels as low as 5 percent. These effects at low CO exposure concentrations, however, have been very small and somewhat controversial. The newer data on neurobehavioral effects of CO has apparently provided little help in resolving this controversy. Nevertheless, the potential consequences of a lapse of coordination, vigilance, and visual sensitivity in the performance of critical tasks by operators of machinery such as public transportation vehicles could be serious. Additional research is, therefore, necessary to provide a better understanding of the mechanisms of action of CO and compensatory changes in the vascular bed that may act to maintain an adequate oxygen supply to the brain.

Certain subgroups of the population are at increased risk from the neural and behavioral effects of elevated COHb. For example, any condition that would reduce oxygen supply to the brain would also potentially exacerbate the effects of CO exposure. A very large subgroup which is known to have a reduced oxygen supply to the brain is the aged. It is, therefore, important to determine COHb dose-response functions for neurobehavioral variables in older subjects. Other conditions that might reduce oxygen supply to the brain include certain cerebrovascular, cardiovascular, and pulmonary disease states mentioned above.

Another large subgroup that may be at increased risk from neurobehavioral effects of CO exposure are those people who take prescription or over-the-counter medications such as antihistamines, sedatives, antipsychotics, antiseizure drugs, antiemetics, and analgesics, that reduce alertness or motor

abilities. The effects of ethanol, caffein, nicotine, and other nonprescription drugs should not be overlooked. Such individuals would be already compromised behaviorally so that any further impairment due to elevated COHb might have serious consequences.

Perinatal Effects

The fetus and newborn infant are theoretically susceptible to CO exposure for several reasons. Fetal circulation is likely to have a higher COHb level than the maternal circulation due to differences in uptake and elimination of CO from fetal hemoglobin. Since the fetus also has a lower oxygen tension in the blood than adults, any further drop in fetal oxygen tension due to the presence of COHb could have a potentially serious effect. The newborn infant with a comparatively high rate of oxygen consumption and lower hemoglobin blood oxygen transport capacity than most adults would also be potentially susceptible to the hypoxic effects of increased COHb. Newer data from laboratory animal studies on the developmental toxicity of CO suggest that prolonged exposure to high levels (>100 ppm) of CO during gestation may produce a reduction in birthweight, cardiomegaly, and delayed behavioral development. Human data are scant and more difficult to evaluate, but further research is warranted. Additional studies are, therefore, needed in order to determine if chronic exposure to CO, particularly at low, near-ambient levels, can compromise the already marginal conditions existing in the fetus and newborn infant.

The effects of CO on maternal-fetal relationships are not well understood. In addition to the fetus and newborn infant, pregnant women also represent a susceptible group because pregnancy is associated with increased alveolar ventilation and an increased rate of oxygen consumption that serves to increase the rate of CO uptake from inspired air. A perhaps more important factor is that pregnant women experience hemodilution due to the disproportionate increase in plasma volume as compared to erythrocyte volume. This group, therefore, should be studied to evaluate the effects of CO exposure and elevated COHb levels.

Population Groups at Greatest Risk for Ambient CO Exposure Effects

Angina patients or others with obstructed coronary arteries, but not yet manifesting overt symptomatology of coronary artery disease, appear to be best established as a sensitive group within the general population that is at increased risk for experiencing health effects (i.e., exacerbation of cardiovascular symptoms) of concern at ambient or near-ambient CO exposure levels. Several other probable risk groups were identified, i.e.: (1) fetuses and young infants; (2) the elderly (especially those with compromised cardiopulmonary or cerebrovascular functions); (3) younger individuals with severe cardiac or acutely severe respiratory diseases; (4) individuals with chronic bronchitis or emphysema; (5) individuals with hematological diseases (e.g., anemia) that affect oxygen carrying capacity or transport in the blood; (6) individuals with genetically unusual forms of hemoglobin associated with reduced oxygen carrying capacity; and (7) individuals using medicinal or recreational drugs having CNS depressant properties. However, little empirical evidence currently is available by which to specify health effects associated with ambient or near-ambient CO exposures in these probable risk groups.

FUTURE RESEARCH NEEDS

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FUTURE RESEARCH NEEDS FOR CARBON MONOXIDE

Current research on carbon monoxide, funded directly or indirectly by EPA, is focusing on: (1) mechanisms of action of CO; (2) cardiovascular effects of CO exposure in patients with angina, arrhythmia, and chronic obstructive pulmonary disease; (3) healthy individuals exposed to CO at high altitudes; and (4) neurotoxicity studies of prenatal CO exposure. Additional EPA-funded research is involved in elucidating dose-response relationships for neurobehavioral effects such as vigilance and coordination tasks in healthy young adults and on validation of the CFKE.

New directions in research on the health effects of carbon monoxide should involve primarily the identification of other potentially susceptible groups in the population beyond those currently being studied. Additional cardiovascular and neurobehavioral studies are needed to determine the dose-response relationships for exposure of potentially susceptible individuals to carbon monoxide and population exposure studies are needed to better quantify the risks that these individuals are exposed to under various ambient conditions. There should also be a continuing effort to validate models predicting COHb levels resulting from exposure to CO, particularly in susceptible individuals exposed at variable concentrations and activity levels. Current research will invoke a renewed interest to (1) identify the mechanisms of action of carbon monoxide; (2) assess the accuracy and reliability of different methods of measuring COHb; and (3) reevaluate previous dose-response functions for CO in probable risk groups utilizing more sensitive methods now available.

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